B7 Cont'd

62.(amended) The solvent vehicle of claim 61, wherein said solvent vehicle comprises glacial acetic acid, dimethylsulfoxide, and an aqueous soy bean lipid emulsion comprising soy bean oil, lecithin, glycerin and water in a 2:6:3 volume ratio.

II. RESPONSE TO OFFICE ACTION

Remarks:

A. Claims in the Case

Claims 26, 34, 36, 38, 48, 49, 53-55, and 60-62 have been amended. Claims 26-68 are presently pending in this case.

B. Support for the Claims

Claim 26 has been amended to include the limitation of "substantially free of organic solvent". Support for this can be found in the specification at various places. For example, page 11, lines 2-6 and lines 21-24, describes that lyophilization "virtually eliminates the organic solvent" of the vehicle, which minimizes side-effects (such as hepatic side-effects) related to the vehicle's organic component. In addition, page 19, lines 5-17, describe that removal of "the major fraction of the organic solvent", such as DMA, allows reconstitution into an aqueous solvent, such as double-distilled water, to obtain a very stable formulation which retained all its pharmacological activity. Furthermore, page 32, lines 10-15, describe the step of lyophilization "virtually eliminates the final-use-preparation's content of the organic solvent". Thus, the amended claim 26 is fully supported by the specification and the amendment does not introduce

any new matter. Therefore, it is intended through the use of the phrase "substantially free of organic solvent" that "the major fraction of the organic solvent" is removed.

Claims 36, 38, 53, 54, 55, 60, 61, and 62 have been amended to generically describe the ingredients of the trademark compositions Intralipid™ and Liposyn II™. The specification generally describes Intralipid™ and Liposyn II™ and no new matter is introduced by this amendment.

Claim 34 has been amended to remove the term "parenteral infusion fluids" and claim 48 has been amended to provide antecedent basis for the term "parenteral infusion fluid". No new matter is added by these amendments.

Claim 49 has been amended to correct a spelling error in the word 'pharmaceutically'. The earlier claim had a typographical error and no new matter is introduced by this amendment.

C. Rejection of Claims Under 35 U. S. C. § 112, Second Paragraph

The Examiner has rejected claims 34, 36, 38, 48, 49, 53-55, and 60-62 under 35 U.S.C. §112, second paragraph as being indefinite.

With regard to claim 34, the Examiner has alleged that distinction between parenteral fluids and the other species listed is not possible.

Applicants respectfully traverse this argument. However, in interest of advancing prosecution, Applicants present amended claim 34, which now lists only the other species of secondary solvents, namely, aqueous lipid emulsion, water, saline solution, dextrose solution, glacial acetic acid, and lipid solution. Applicants also present an amendment to claim 48, which now recites that secondary solvent comprises a parenteral fluid. Applicants believe that these

amendments satisfy the 35 U.S.C. §112, second paragraph requirement, and request withdrawal of this rejection.

The Examiner has alleged that claims 36, 38, 53-55, and 60-62 are indefinite under 35 U.S.C. §112, as they recite trademark names.

With respect to these claim rejections, Applicants present claim amendments to claims 36, 38, 53-55, and 60-62, to generically describe the ingredients of the trademark compositions, Intralipid™ and Liposyn II™, recited in the claims. It is well known to one of skill in the art that Intralipid™ is an aqueous lipid emulsion comprising soy bean oil, lecithin, glycerin and water, and that Liposyn II™ is another aqueous lipid emulsion that comprises emulsified fat particles of about 0.4 micron in diameter. In view of these amendments, Applicants believe that claims 36, 38, 53-55, and 60-62 are now in compliance with the 35 U.S.C. §112, second paragraph requirements and request withdrawal of these rejections.

In regard to the rejection to claim 49, the Examiner alleges that the different species listed in the claim are mutually non-exclusive.

Applicants respectfully traverse and present that the standard to determine the definiteness of the claim is whether the claim meets the threshold requirements of clarity and precision and whether the scope of the claim is clear to the skilled artisan (see M.P.E.P. 2171 and 2173.02). In *In re Wiggins,* 488 F2d 538, 179 USPQ 421 (CCPA 1973), it was shown that a rejection of claims under U.S.C. 112, second paragraph is appropriate only if the scope of the invention sought to be patented cannot be determined from the language of the clams with a reasonable degree of certainty. The standard therefore, is whether one of ordinary skill in the art can understand each of the species recited in the claim. The different species listed in claim 49

include, an active agent, a drug, a pharmaceutically acceptable carrier, an adjuvant, or a biologically active substance. Applicants present that these distinct groups are readily comprehensible to the skilled man. In fact, a skilled artisan will readily appreciate that the solvent vehicle of the invention can additionally comprise any of the different species listed above. Furthermore, the M.P.E.P., in 2173.02, also sets forth that Applicants "may use functional language, **alternative expressions**, negative limitations, or any style of expression or format of claim which makes clear the boundaries of the subject matter for which protection is sought" (**emphasis added**). As noted by the Court in *In re Swinehart,* 439 F.2d 210, 160 USPQ 226 (CCPA 1971), a claim may not be rejected solely because of the language used to define the subject matter for which protection is sought. Applicants present that the different species recited in claim 49 are clearly set forth in the claim, and easily understood by one of skill in the art. In view of this, Applicants contend that there is no question of the terms being indefinite and request withdrawal of this rejection.

The Examiner also alleges that in claims 65 and 66 the term parenteral is all inclusive.

Applicants are not clear as to the requirement of this rejection. Applicants would like to clarify that claim 65 describes administration of the composition by parenteral injection, and claim 66, which properly depends on claim 65, further describes the type of parenteral injections as intravascular injections or intravenous injections. Claim 66 properly includes all the limitations of claim 65 and further properly narrows what is claimed by claim 65. Applicants present that both these claims in question are definite, and that claim 66 is properly dependent on claim 65. Therefore, Applicants request the withdrawal of this rejection.

D. Rejection of Claims Under 35 U. S. C. § 112, First Paragraph

The Examiner has rejected claim 68 under 35 U. S. C. § 112, first paragraph, as containing subject matter not described in the specification to enable one of skill in the art to make and/or use the invention and specifically pointed to the alleged absence of description of lyophilization of vehicles in the specification.

Applicants traverse this rejection and point that the specification provides ample description of lyophilizable vehicles. For example, page 5, lines12-18, describe the steps of lyophilization and state:

> In one preferred embodiment, the method further includes the step of lyophilizing the composition, whereby the majority of the water and the aprotic solvent (e.g., more than 50%, preferably more than 95%, and most preferably more than 99% by weight) are removed from the composition and a dry, shelf-stable composition is produced. This dry composition can be reconstituted into an aqueous solution suitable for parenteral administration to a mammal, by adding to the dry composition a pharmaceutically acceptable aqueous solvent.

In addition, page 11, lines 2-5, describes the utility of the lyophilization step to remove the vehicle's organic component and states that:

> The addition of a lyophilization step virtually eliminates the organic solvent, DMA, from the final clinical "working solution", and it should abolish the potential for adverse reactions related to the DMA, and minimize the possibility for a potentiation of (hepatic) side effects from the combination of DMA and pimaricin. This added step should therefore assist in maximizing patient safety after drug administration.

Lyophilization is also described in the Examples, for example, in Example 1, page 19, lines 13-26, which describes the stability of the composition following lyophilization to remove organic solvents such as DMSO. In addition, in Example 2, page 20, lines 10-13, describe reconstitution after lyophilization to obtain isosmotic vehicles and page 21, lines 6-9, describe

lowering of hemolytic potential of lyophilized formulations of the invention. Furthermore, Example 3, also describes the steps of lyophilization at various places, see pages 22-23, as does Example 4, on page 32, lines 10-15.

In light of this, Applicants present that claim 68 is fully enabled and request removal of the rejection to claim 68.

E. Rejection of Claims Under 35 U.S.C. § 102 and 35 U.S.C. § 103

The Examiner has also rejected claims 26-28, 30-34, 41-45, 47-52, 57-59, and 63-67 as anticipated by Andersson et al 5,559,148, under 35 U.S.C. § 102(e), and by Andersson et al 5,430,057, under 35 U.S.C. § 102(b), alleging that solvent vehicles comprising ingredients and concentrations described by the instant invention. The Examiner has also rejected claims 26, 27, 29, 32, 34, 35, 37-42, 47-49 and 63-68 as anticipated by U.S. Patent 5,651,991, to Sugiyama et al, under 35 U.S.C. § 102(e).

Regarding the anticipation rejections made on basis of the 5,559,148, and the 5,430,057, patents Applicants respectfully traverse. In order to clarify the instant solvent vehicles and to facilitate prosecution of the instant case, Applicants present amended claim 26. Amended claim 26, recites that the solvent vehicle of the instant invention are "substantially free of organic solvents". Both the 5,559,148 and the 5,430,057 patents describe parenteral formulations for administration of busulfan. However, those formulations also comprise organic solvent. For example, in 5,559,148, column 4, lines 13-24, describe that the solvent may comprise N'N-dimethylacetamide (DMA), or PEG; and column 4, lines, 44-57, describes that other organic solvents such as propylene glycol or hydroxypropylbetacyclodextrin may be comprised in those solvents and lists the concentrations of those organic solvents in the final formulation. The

presence of organic solvents in the busulfan formulations is also described in column 6, lines 15-29 and in several places in the Examples in columns 7-19.

Again, in 5,430,057, column 4, lines 16-29, describe that the solvent may comprise N'N-dimethylacetamide (DMA), or PEG; and column 4, lines, 40-63, describes that other organic solvents such as propylene glycol or hydroxypropylbetacyclodextrin may be comprised in those solvents and lists the concentrations of those organic solvents in the final formulation. The presence of organic solvents in the busulfan formulations is also described in column 6, lines 2-44 and in several places in the Examples in columns 7-19.

In stark contrast, the present application, provides vehicles that are substantially free of organic solvents and this is fully supported in the specification. For example, page 11, lines 2-5 specifically describes the removal of organic components, such as DMA, and states that:

> The addition of a lyophilization step **virtually eliminates the organic solvent, DMA, from the final clinical "working solution",** and it should abolish the potential for adverse reactions related to the DMA, and minimize the possibility for a potentiation of (hepatic) side effects from the combination of DMA and pimaricin. This added step should therefore assist in maximizing patient safety after drug administration. **(emphasis added)**

In another example, the present specification, in Example 1, page 19, lines 5-26, describes that removal of organic solvents such as DMSO, improves stability of the final composition, and states:

> The **major fraction of the organic solvent, DMA, was removed** by lyophilization of the pimaricin/DMA/aqueous lipid complex to create a solvate that was stable yet easily reconstituted by adding only double-distilled water under gentle agitation with out any appreciable loss of anti-fungal efficacy. Indeed, within a few minutes after addition of distilled water to the solvate, the drug was reconstituted at 1-10 mg/ml, **with only trace amounts of the organic solvents remaining**. This reconstituted pimaricin formulation retained an anti-fungal efficacy that was equivalent to that of freshly prepared DMA/aqueous lipid formulation and was also

> stable at 4°C for more than 2 weeks. The lyophilized pimaricin formulation remained stable (by HPLC) for more than four months at 4°C. This preparation could still be readily reconstituted to 10 mg/ml within a few minutes with distilled water, with retention of full anti-fungal activity *in vitro* (see Tables 3 and 4 below).
> We further simulated a final clinical use-formulation with a pimaricin solution of 1 mg/ml by dilution the 10 mg/ml-formulations (prepared fresh with DMA/Intralipid or after lyophilization/reconstitution respectively) with 5% dextrose or NS. Figure 5 shows the respective stability at RT of the "use-formulations". Similarly, when HAc and DMSO were used as the primary solvent system prior to mixing with Intralipid and followed by lyophilization, **the majority of the organic solvent, here DMSO, was removed** and the result was a stable lipid-based solvate, that could be easily reconstituted to 10 mg/ml under gentle agitation after the addition of distilled water. **(emphasis added)**

In view of this, Applicants contend that the present solvent vehicles are distinct over the art and request withdrawal of these rejections.

With regard to the anticipation rejections made by the Examiner in view of U.S. Patent 5,651,991, Applicants again respectfully traverse. The 5,651,991 reference only describes drug carriers that comprise a fatty emulsion. In contrast the present invention describes solvent vehicles that comprise a pharmaceutically acceptable dipolar aprotic solvent and a pharmaceutically acceptable aqueous secondary solvent, which further are substantially free of organic solvent. In some embodiments the aqueous secondary solvent of the present invention comprises a lipid emulsion. The 5,651,991, reference does not describe dipolar aprotic solvents and more importantly does not describe the absence of organic solvents from the final composition. On the other hand, the instant specification teaches removal of virtually all of the organic component of the vehicles of the invention, and also demonstrates how this makes the vehicle extremely useful. For example, page 11, lines 2-5, describes how the removal of organic solvent, reduces the adverse effects related to organic solvents, such as hepatic side effects,

maximizing patient safety after drug administration. In other examples, page 19, lines 13-26, describes the increased stability and longer shelf life following removal of organic solvents such as DMSO; page 20, lines 10-13, teach how to make isosmotic vehicles by reconstitution following lyophilization to remove organic solvents; and page 21, lines 6-9, describes other beneficial effects such as lowering of hemolytic potential of lyophilized formulations in which organic solvents are removed. Thus, the vehicles of the present invention are distinct and novel over the cited art.

In view of this, Applicants present the pending claims are novel and the Examiner is requested to withdraw the 35 U.S.C. § 102 rejections.

F. Rejection of Claims Under 35 U.S.C. § 103

The Examiner has also presented an obviousness rejection to claims 26-68 under 35 U.S.C. § 103(a) as being unpatentable over the 5,430,057 patent to Andersson et al, in view of the 5,651,991 patent to Sugiyama et al.

Applicants respectfully traverse. As set forth above, in order to facilitate prosecution of the instant case and to clarify the instant solvent vehicles, Applicants present amended claim 26. The solvent vehicles of the present invention are distinguished in that they are "substantially free of organic solvents".

Both the 5,430,057 and the 5,651,991 references and their differences with the present invention are described above, in the discussion of the U.S.C. § 102 rejections. Briefly, while the 5,430,057, patent provides busulfan formulations that contain organic solvents such as DMA, PEG, propylene glycol *etc.*, the 5,651,991, patent describes drug carriers that comprise lipid emulsions. The instant invention, however, provides solvent vehicles that comprise a dipolar

aprotic solvent, in which a drug or pharmaceutical agent is first dissolved in, and a aqueous secondary solvent, into which the agent is further dissolved, which is then rendered substantially free of organic solvent. As 5,430,057, describes formulations that do comprise organic solvents, the present application is completely distinct. Therefore, the obviousness rejection made in view of 5,430,057 are not valid.

Regarding the secondary reference, 5,651,991, that reference only describes drug carriers that are composed of lipid based emulsions. There is no teaching here or in any other reference of the absence or removal of organic solvents from the final composition. Thus, this reference is completely unrelated to the present invention.

In addition, as described above, the solvent vehicles of the instant invention provide numerous clinically useful properties, on account of being substantially free of organic solvents, for example, minimized side effects caused by organic solvents after administration to patients; increased stability and shelf-life; lowered hemolytic properties; ability to obtain isosmotic vehicles; *etc.* which make them superior to other compositions. Thus, Applicants present that the obviousness rejection is moot and request withdrawal of this rejection.

III. CONCLUSION

In light of the above, the Examiner is requested to reconsider the pending rejections. It is submitted that the present response is a complete response, and that the claims are now in condition for allowance. Attached herewith, for the convenience of the Examiner are, a marked-up version of the amended claims in **Appendix A** and a clean copy of the pending claims in **Appendix B**. If the Examiner has any questions or comments, he is earnestly requested to contact the undersigned representative.

Respectfully submitted,

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APPENDIX A

MARKED-UP VERSION OF AMENDED CLAIMS

26.(amended) A solvent vehicle, comprising a pharmaceutically acceptable dipolar aprotic solvent and a pharmaceutically acceptable aqueous secondary solvent [.] , substantially free of organic solvent.

34.(amended) The composition of claim 26, wherein said secondary solvent comprises aqueous lipid emulsion, water, saline solution, dextrose solution, glacial acetic acid, or lipid solution. [or parenteral infusion fluids.]

36.(amended) The solvent vehicle of claim 35, wherein said aqueous lipid emulsion comprises [Liposym II™] emulsified fat particles of about 0.4 micron in diameter.

38.(amended) The solvent vehicle of claim 37, wherein said aqueous soy bean lipid emulsion comprises [Intralipid™] soy bean oil, lecithin, glycerin and water.

48.(amended) The solvent vehicle of claim 26, wherein said secondary solvent comprises a parenteral infusion [fluids] fluid.

49.(amended) The solvent vehicle of claim 26, wherein said composition further comprises an active agent, a drug, [pharnaceutically] pharmaceutically acceptable carriers, adjuvants or biologically active substances.

53.(amended) The solvent vehicle of claim 52, wherein said aqueous lipid is [Intralipid™] an aqueous soy bean lipid emulsion comprising soy bean oil, lecithin, glycerin and water.

54.(amended) The solvent vehicle of claim 53, wherein said solvent vehicle comprises anhydrous N,N,-dimethylacetamide and [Intralipid™] an aqueous soy bean lipid emulsion comprising soy bean oil, lecithin, glycerin and water in a 1:10 volume ratio.

55.(amended) The solvent vehicle of claim 53, wherein said solvent vehicle comprises anhydrous N,N,-dimethylacetamide diluted with 9 volumes 20% [Intralipid™] of an aqueous soy bean lipid emulsion comprising soy bean oil, lecithin, glycerin and water.

60.(amended) The solvent vehicle of claim 26, wherein said vehicle comprises glacial acetic acid, and wherein said vehicle further comprises anhydrous N,N,-dimethylacetamide, dimethylsulfoxide or [Intralipid™] an aqueous soy bean lipid emulsion comprising soy bean oil, lecithin, glycerin and water.

61.(amended) The solvent vehicle of claim 26, wherein said solvent vehicle comprises glacial acetic acid, dimethylsulfoxide and [Intralipid™] an aqueous soy bean lipid emulsion comprising soy bean oil, lecithin, glycerin and water.

62.(amended) The solvent vehicle of claim 61, wherein said solvent vehicle comprises glacial acetic acid, dimethylsulfoxide, and [Intralipid™] an aqueous soy bean lipid emulsion comprising soy bean oil, lecithin, glycerin and water in a 2:6:3 volume ratio.